110. (New) The system of claim 65, wherein the analyte is a protein, a peptide or a nucleic acid.

111. (New) The method of claim 87, wherein the analyte is a biomolecule.

112. (New) The method of claim 87, wherein the analyte is a biomolecule from an undifferentiated sample.

113. (New) The method of claim 87, wherein the analyte is a protein, a peptide or a nucleic acid. --

REMARKS

Status of the Application

Claims 49-113 are pending with entry of this amendment, with claims 1 and 42-48 being canceled and claims 102-113 being added herein.

Claims 32-63 and 86-101 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-20 of U.S. Patent No. 5,719,060. Claims 32-101 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-24 of copending Application No. 08/068,896. Claims 32, 49, 64 and 86 were rejected under 35 U.S.C. §102 over Applicants' allegedly admitted prior art, Stuke or Zare *et al.* Claims 32-101 were rejected under 35 U.S.C. §102 over Humpel *et al.* or Turteltaub *et al.* Claims 33-48, 50-63, 65-68 and 87-101 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Applicants' disclosure or Stuke in view of Turteltaub *et al.*

Support for Amendments

Support for the amendments to the claims can be found throughout the specification and the claims, as originally filed. For example, support for amendment to claim 32 can be found on, *e.g.*, page 12, line 19 of the specification. Support for amendments to claims 49, 50, 52, 64, 65, 86, 87 and 90 can be found on, *e.g.*, page 11, line 8 of the specification and originally filed claim 1. Support for new claims 102-113 can be found on, *e.g.*, page 8, lines 16-18, page 10, lines 17-19, page 12, last line to page 13, line 1 of the specification and originally filed claim 9. Applicants have altered the dependencies of some of the claims merely in order to specifically claim certain embodiments of the invention. The amendments do not introduce new matter.

As a convenience to the Examiner, a complete set of the pending claims is attached to this response as an appendix.

A Copy of Considered IDS Requested

The Office Action Summary indicates that a copy of the Information Disclosure Statement (IDS), Paper No. 3, was attached to the Office Action. It is noted that Applicants have not received a copy of the considered Information Disclosure Statement (IDS). Applicants respectfully request that the Examiner provide Applicants a copy of the considered IDS with the next Office Action.

Supplemental IDS

A supplemental IDS is enclosed with this response, which cites Van Breemen *et al.*, *Intern. J. of Mass Spectr. and Ion Physics* 49:35-50 (1983). Applicants note that Van Breemen *et al.* desorbs "preformed ions" (*i.e.*, ions existing prior to exposure to an energy source, such as salts) from the probe surface using a laser. Neutral species that remain un-ionized when exposed to laser are then ionized with a secondary ionizing energy source. Van Breenmen *et al.* does not teach or suggest desorbing and ionizing analytes using a single energy source in a mass spectrometer as in the present invention.

Obviousness-type Double Patenting Rejections

Claims 32-63 and 86-101 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-20 of U.S. Patent No. 5,719,060. Claims 32-101 were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 08/068,896.

These rejections are traversed. However, Applicants note that the '060 patent has an apparent patent term through February 17, 2015, and a patent issuing from Application No. 08/068,896 (which is on appeal) would normally expire 17 years from the date of issue. A patent issuing from the present application would normally expire on May 28, 2013. Therefore, Applicants expect no loss in patent term as a result of filing terminal a disclaimer in the present application. Without agreeing with the substance of the Examiner's rejection and in the interest of expediting the prosecution, Applicants will submit a terminal disclaimer upon an indication that the claims are otherwise allowable, provided such a disclaimer are appropriate for any such claims.

The Rejections Under 35 U.S.C. §102

A. The Description of the Prior Art Section in the Specification

Claims 32, 49, 64 and 86 were rejected under 35 U.S.C. §102(a) as being anticipated by Applicants' allegedly admitted prior art. According to the Examiner, pages 1-5 of the specification describe a method/apparatus "having a spectrometer tube, vacuum means, electrical potential means for accelerating a portion of the disturbed sample, a probe for presenting the sample where a portion (not all) of the sample is used, a laser and detector. Clearly the matrix in which the sample associated is an energy absorbing means since a portion of the matrix is vaporized (*i.e.* the matrix has absorbed energy to change its physical state)."

Applicants respectfully traverse the rejection, because anticipation has not been established. "For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference." *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). If the examination at the initial stage does not produce a *prima*

facie case of unpatentability, then without more, the applicant is entitled to the grant of a patent. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Claims 32, 49, 64 and 86, as previously presented or currently pending, were not anticipated, because every element of the rejected claims was not identically shown in the Description of the Prior Art Section of the specification. For example, claim 32 was directed to a probe for a mass spectrometer, wherein its surface comprises "a non-metallic material" and claims 49, 64 and 86 were directed to methods of desorbing an analyte, a system, or methods for detecting an analyte comprising a probe having a non-metallic surface. It was never admitted by Applicants that a probe comprising, *inter alia*, a non-metallic surface is a feature known in the prior art. Rather, page 2, lines 6-7 of the specification states that in the known prior art procedures, analytes were deposited on "the bare surface of a metallic probe tip." Since the Description of the Prior Art Section of the specification does not disclose every element of claims 32, 49, 64 and 86, the rejection of the claims is improper, and withdrawal of the rejection is respectfully requested.

B. Humpel et al. (U.S. Patent 5,124,267)

Claims 32-101 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Humpel *et al.* The carryover paragraph of pages 4-5 of the Office Action states that "Humpel *et al.* teaches a method and apparatus indistinguishable from the instant claims where an analyte is immobilized and subjected to spectroscopic ** analysis. In column 2 various substrates upon which the sample can be immobilized on are taught that read on the instant probe." Applicants respectfully traverse this rejection.

Claims 32-101, as previously presented or currently pending, were not anticipated by Humpel *et al.*, because every element of the claims was not disclosed in Humpel *et al.* In rejecting the claims, the Office Action appears to rely upon column 2, lines 23-26 of Humpel *et al.* which states that "polymeric substrate materials are used as the stationary phase, such as, for example, sepharose, cellulose, 'Carbopol', silica gel, or Al_2O_3 ($\times x$ H_2O)." However, the alleged polymeric substrate referred to in the cited passage is not a probe for a mass spectrometer. Rather, the alleged polymeric substrate material is merely used to capture a compound of

interest. The compound is subsequently eluted from the alleged substrate. After elution, the compound is then subject to GC/MS analysis. *See*, Example 3 at column 6. Thus, the alleged polymeric substrate is used only prior to GC/MS analysis and is not a probe for a mass spectrometer.

Humpel *et al.* does not disclose the details of a probe for a mass spectrometer. For example, column 2, lines 36-40 state "[m]easurement in a mass spectrometer has, in the meantime, evolved into being part of the daily routine and thus requires no detailed explanation." (emphasis added). Accordingly, "no detailed explanation" of Humpel *et al.*'s mass spectrometry apparatus or probe appears to be provided. As such, Humpel *et al.* does not disclose, *inter alia*, a probe that is removably insertable into a mass spectrometer, let alone a probe with a non-metallic surface as recited in claims 32, 49, 64 or 86. Since Humpel *et al.* does not disclose every element of the independent claims, Humpel *et al.* does not anticipate the claims and the rejection is improper.

Moreover, anticipation has not been established with respect to the dependent claims, because they depend upon novel and unobvious independent claims. In addition, the dependent claims recite additional limitations that are not taught by Humpel *et al.* For example, Humpel *et al.* does not disclose a system comprising a probe surface which is adhered to the probe magnetically as recited in claim 72. In another example, Humpel *et al.* does not disclose a system comprising a probe surface comprising metal coated with a synthetic polymer as recited in claim 73. In yet another example, Humpel *et al.* does not disclose a system comprising a probe having a synthetic polymer as a surface coating as recited in claim 74. Therefore, the rejection of the dependent claims is also improper, and withdrawal of the rejection is respectfully requested.

C. Stuke (U.S. Patent 4,868,366)

Claims 32, 49, 64 and 86 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Stuke. According to the Office Action, Stuke teaches "a time of flight mass spectrometer for the analysis of biological samples that are bound to a sample probe when inserted into the mass spectrometer." Applicants respectfully traverse this rejection.

Claims 32, 49, 64 and 86 were not anticipated by Stuke, because every element of the claims was not disclosed by Stuke. Stuke discloses a laser mass spectrometer comprising an electrode system and an ion detector means both mounted on a support flange adapted to be sealed to a port of a vacuum apparatus. *See, e.g.*, the cover picture and the abstract. However, there is no disclosure in Stuke, *inter alia*, a probe that is removably insertable into a mass spectrometer, let alone a probe with a surface that comprises a non-metallic material as recited in claims 32, 49, 64 and 86. In fact, column 2, lines 31-33 of Stuke state that the vacuum system in which the substance to be investigated by mass spectrometry is "not shown," thus indicating that no detailed description of the sample presentation means is provided by Stuke. Since Stuke does not disclose every element of the claims, the rejection is improper, and withdrawal of the rejection is respectfully requested.

D. Zare et al. (U.S. Patent 4,988,879)

Claims 32, 49, 64 and 86 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Zare *et al.* Page 5 of the Office Action states that Zare *et al.* teaches "a time of flight mass spectrometer for the analysis of biological samples that are bound to a sample probe when inserted into the mass spectrometer." Applicants respectfully traverse this rejection.

Zare *et al.* does not anticipate the presently claimed invention. For example, independent claims 49, 64 and 86 recite a method of desorbing an analyte, a system, or a method for detecting an analyte, respectively, using a single energy source that directs energy to the probe surface for "desorbing and ionizing" an analyte. By contrast, Zare *et al.* requires two separate energy sources - a desorption laser to desorb analytes and an ionizing laser to ionize the analytes. As stated at column 10, lines 23-30, an element of Zare *et al.*'s methodology is "the spatial and temporal separation and desorption and ionization. This allows one to select the energies and pulse durations for each of these two steps independently." Thus, Zare *et al.*'s systems and methods are completely different from the presently claimed systems and methods that use a single energy source to desorb and ionize an analyte. Since Zare *et al.* does not disclose every element of the claims, the rejection is improper and withdrawal of the rejection is respectfully requested.

E. Turteltaub et al. (U.S. Patent 5,209,919)

Claims 32-101 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Turteltaub *et al.* According to the Office Action, "Turteltaub teaches a mass/apparatus time of flight mass spectrometer for the analysis of biological samples that are bound to a sample probe when inserted into the mass spectrometer similar to that presently claimed." Applicants respectfully traverse this rejection.

Claims 32-101, as previously presented or currently pending, were not anticipated by Turteltaub *et al.* For example, Turteltaub *et al.* does not teach a probe having a non-metallic surface for presenting samples as recited in claim 32. Rather, Turteltaub *et al.* discloses using an aluminum or other suitable material planchet to present samples to the ion source in the accelerator mass spectrometer. *See*, column 23, line 46. Turteltaub *et al.* also does not disclose, *inter alia*, methods of desorbing an analyte, a system, or methods for detecting an analyte that utilizes a probe having a non-metallic surface as recited in 49, 64 and 86. Since Turteltaub *et al.* does not disclose every element of the claimed invention, Turteltaub *et al.* does not anticipate the claimed invention.

Moreover, anticipation has not been established with respect to the dependent claims, because they depend upon novel and unobvious independent claims. In addition, the dependent claims recite additional limitations that are not taught by Turteltaub *et al.* For example, Turteltaub *et al.* does not disclose a system comprising a probe surface which is adhered to the probe magnetically as recited in claim 72. In another example, Turteltaub *et al.* does not disclose a system comprising a probe surface comprising metal coated with a synthetic polymer as recited in claim 73. In yet another example, Turteltaub *et al.* does not disclose a system comprising a probe comprising a synthetic polymer as a surface coating as recited in claim 74. Therefore, the rejection of the dependent claims is also improper, and withdrawal of the rejection is respectfully requested.

Finally, it is noted that Turteltaub *et al.*'s methods are completely different from the present invention. Rather than analyzing biological samples that are bound to a probe for a mass spectrometer as in the present invention, Turteltaub *et al.* discloses combusting labeled biological samples, pressing the resulting material into a sample holder, and measuring radio-isotopes using

accelerator mass spectrometry (*see, e.g.*, Example 1). Thus, in Turteltaub *et al.*'s methods, biological samples were completely destroyed by the combustion process, and Turteltaub *et al.* does not disclose presenting biological samples on a probe surface for mass spectrometry analysis as in the present application.

The Rejection under 35 U.S.C. §103

Claims 33-48, 50-63, 65-68 and 87-101 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Applicants' disclosure (*see* pages 1-5) or Stuke further in view of Turteltaub *et al.* According to the Examiner, Applicants' allegedly admitted Description of the Prior Art section and Stuke disclose a time-of-flight mass spectrometer for the analysis of biological samples that are bound on a probe surface, but they are "silent with respect to the specific types of binding materials." The Examiner further states that "Turteltaub *et al.* teaches that small amounts of specific biological samples can be obtained by an affinity type of reaction. This type of sample acquisition is advantageous because very specific substance for analysis can be obtained through this affinity binding collection techniques. It would have been well within the skill of the art to modify the method/apparatus taught by Applicants' disclosure (*see* pages 1-5) or Stuke in view of Turteltaub *et al.* and use affinity binding techniques to collect the samples to gain the advantages taught above." *See* pages 6-7 of the Office Action. Applicants respectfully traverse the rejection.

Initially, it is noted that Applicants have addressed Stuke or Turteltaub *et al.* in several related applications and successfully overcame all of the rejections based on these references. Moreover, it is noted the use of affinity binding techniques in mass spectrometry is not a claimed feature of the present application, contrary to the Examiner's apparent belief. Rather, claimed features include systems and methods comprising, *inter alia*, a probe for a mass spectrometer with a non-metallic surface and a single energy source for desorption and ionization.

A *prima facie* case of obviousness has not been established, because none of the cited references or the Description of the Prior Art section in the specification, alone or in combination, do not teach or suggest all the limitations in the claims. To establish *prima facie*

obviousness, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). MPEP §2143.03.

Here, obviousness has not been established, because none of the cited references or the Description of the Prior Art section in the specification disclose, *inter alia*, systems and methods for detecting an analyte comprising a probe that is removably insertable into a mass spectrometer, wherein the probe surface comprises non-metallic surface as recited in the present claims. For example, the Description of the Prior Art section in the specification states that in the known prior art procedures, "a bare surface of a metallic probe tip" was used. Stuke does not even provide any description for a probe for a mass spectrometer, as it is not the focus of his invention. Turteltaub *et al.* fails to cure these deficiencies. Turteltaub *et al.* discloses using aluminum or other suitable material planchet to present samples to the ion source, not a probe with a non-metallic surface as in the present application. Moreover, as described above, Turteltaub *et al.*'s methods are completely different from the present invention. Because the cited references or the Description of the Prior Art section of the present application, alone or in combination, do not teach or suggest all of the claim limitations, a *prima facie* case of obviousness has not been established.

CONCLUSION

Applicant believes that there is no additional fee required to file this paper. If Applicant is in error, the Commissioner is hereby authorized to charge any required fees and/or credits by this paper and during the entire pendency of this application to Account No. 06-2375/D-5639/09306611.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 713-651-5325.

Respectfully submitted,

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APPENDIX

49. A method of desorbing an analyte from a probe surface comprising the steps of:

(a) providing a probe that is removably insertable into a mass spectrometer, the probe having a surface for presenting the analyte to an energy source that emits energy capable of desorbing and ionizing the analyte from the probe for analyte detection, wherein at least the surface comprises a non-metallic-material, and wherein the analyte is on the probe surface; and

(b) exposing the analyte to energy from the energy source, whereby the analyte is desorbed and ionized.

50. The method of claim 49 wherein the energy source emits laser light that desorbs and ionizes the analyte to produce an ion.

51. The method of claim 50 further comprising after step (b) the steps of:

c) modifying the analyte chemically or enzymatically while deposited on the probe surface; and

d) repeating step (b).

52. The method of claim 50 wherein the probe surface comprises an array of locations, each location having at least one analyte deposited thereon; and step (b) comprises desorbing and ionizing a first analyte from a first location in the array;

and wherein the method further comprises the step of (c) desorbing and ionizing a second analyte, from a second location in the array.

53. The method of claim 50 further comprising before step (b) the step of modifying the analyte chemically or enzymatically while deposited on the probe surface.

54. The method of claim 50 wherein the surface comprises metal coated with a synthetic polymer, glass, ceramic, a synthetic polymer or a mixture thereof.

55. The method of claim 50 wherein the surface is coated with a synthetic polymer.

56. The method of claim 50 wherein the non-metallic material is substantially porous.

57. The method of claim 50 wherein the non-metallic material is substantially non-porous.

58. The method of claim 50 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially porous material.

59. The method of claim 50 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially non-porous material.

60. The method of claim 50 wherein the probe comprises glass.

61. The method of claim 50 wherein the probe comprises ceramic.

62. The method of claim 50 wherein the probe comprises a synthetic polymer.

63. The method of claim 50 wherein the analyte comprises protein.

64. A system for detecting an analyte comprising:

a removably insertable probe having a surface for presenting the analyte to an energy source that emits energy capable of desorbing and ionizing the analyte from the probe, wherein at least the surface comprises a non-metallic material, and an analyte on the surface;

an energy source that directs energy to the probe surface for desorbing and ionizing the analyte; and

a detector in communication with the probe surface that detects the desorbed analyte.

65. The system of claim 64 which is a laser desorption mass spectrometer wherein:

the energy source emits laser light that desorbs and ionizes the analyte to produce an ion,

the system further comprises means for accelerating the ion to the detector,

the detector detects the ion, and

the system further comprises means for determining the mass of the ion.

66. The system of claim 64 wherein the energy source emits laser light.

67. The system of claim 64 wherein the energy source emits plasma energy or fast atoms.

68. The system of claim 64 wherein the energy source emits energy of a variety of wavelengths.

69. The system of claim 64 wherein the detector detects ions.

70. The system of claim 64 wherein the detector detects radioactivity or light.

71. The system of claim 64 further comprising means for accelerating the desorbed analyte to the detector.

72. The system of claim 65 wherein the surface is adhered to the probe magnetically.

73. The system of claim 65 wherein the surface comprises metal coated with a synthetic polymer, glass, ceramic, a synthetic polymer or a mixture thereof.

74. The system of claim 65 wherein the surface is coated with a synthetic polymer.

75. The system of claim 65 wherein the non-metallic material is substantially porous.

76. The system of claim 65 wherein the non-metallic material is substantially non-porous.

77. The system of claim 65 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially porous material.

78. The system of claim 65 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially non-porous material.

79. The system of claim 65 wherein the probe comprises glass.

80. The system of claim 65 wherein the probe comprises ceramic.

81. The system of claim 65 wherein the probe comprises a synthetic polymer.

82. The system of claim 75 wherein the porous material comprises sponge-like, polymeric, high surface areas.

83. The system of claim 76 wherein the non-porous material is selected from the group consisting of glass and polyacrylamide.

84. The system of claim 77 wherein the porous material comprises sponge-like, polymeric, high surface areas.

85. The system of claim 78 wherein the non-porous material is selected from the group consisting of glass and polyacrylamide.

86. A method for detecting an analyte comprising the steps of:

a) providing a system comprising:

(1) a removably insertable probe having a surface for presenting the analyte to an energy source that emits energy capable of desorbing and ionizing the analyte from the probe, wherein at least the surface comprising a non-metallic material, and an analyte on the surface;

(2) an energy source that directs energy to the probe surface for desorbing and ionizing the analyte; and

(3) a detector in communication with the probe surface that detects the desorbed and ionized analyte;

b) desorbing and ionizing at least a portion of the analyte from the surface by exposing the analyte to the energy; and

c) detecting the desorbed and ionized analyte with the detector.

87. The method of claim 86 wherein the system is a laser desorption mass spectrometer wherein the energy source emits laser light that desorbs and ionizes the analyte to produce an ion, the detector detects the ion and the system further comprises means for accelerating the ion to the detector, and the method further comprises determining the mass of the ion.

88. The method of claim 87 further comprising before step (b) the step of modifying the analyte chemically or enzymatically while deposited on the probe surface.

89. The method of claim 87 further comprising after step (c) the steps of:

d) modifying the analyte chemically or enzymatically while deposited on the probe surface; and

e) repeating steps b) and c).

90. The method of claim 87 wherein the probe surface comprises an array of locations, each location having at least one analyte deposited thereon; and step (b) comprises desorbing and ionizing a first analyte from a first location in the array;

and wherein the method further comprises the step of:

d) desorbing and ionizing a second analyte from a second location in the array; and

e) detecting the desorbed and ionized second analyte with the detector.

91. The method of claim 87 further comprising the step of displaying the determined mass of the analyte.

92. The method of claim 87 wherein the surface comprises metal coated with a synthetic polymer, glass, ceramic, a synthetic polymer or a mixture thereof.

93. The method of claim 87 wherein the surface is coated with a synthetic polymer.

94. The method of claim 87 wherein the non-metallic material is substantially porous.

95. The method of claim 87 wherein the non-metallic material is substantially non-porous.

96. The method of claim 87 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially porous material.

97. The method of claim 87 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially non-porous material.

98. The method of claim 87 wherein the probe comprises glass.

99. The method of claim 87 wherein the probe comprises ceramic.

100. The method of claim 87 wherein the probe comprises a synthetic polymer.

101. The method of claim 87 wherein the analyte comprises protein.

102. The method of claim 62 wherein the synthetic polymer comprises polystyrene, polypropylene, polyethylene, polycarbonate, or biopolymers.

103. The system of claim 81 wherein the synthetic polymer comprises polystyrene, polypropylene, polyethylene, polycarbonate, or biopolymers.

104. The method of claim 100 wherein the synthetic polymer comprises polystyrene, polypropylene, polyethylene, polycarbonate, or biopolymers.

105. The method of claim 50, wherein the analyte is a biomolecule.

106. The method of claim 50, wherein the analyte is a biomolecule from an undifferentiated sample.

107. The method of claim 50, wherein the analyte is a protein, a peptide or a nucleic acid.

108. The system of claim 65, wherein the analyte is a biomolecule.

109. The system of claim 65, wherein the analyte is a biomolecule from an undifferentiated sample.

110. The system of claim 65, wherein the analyte is a protein, a peptide or a nucleic acid.

111. The method of claim 87, wherein the analyte is a biomolecule.

112. The method of claim 87, wherein the analyte is a biomolecule from an undifferentiated sample.

113. The method of claim 87, wherein the analyte is a protein, a peptide or a nucleic acid.